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16. ABSTRACT

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with specific chemicals or compounds. The Office of Emergency and Remedial Response (Superfund) uses these documents in preparing cost-benefit analyses under Executive Order 12991 for decision-making under CERCLA. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data are available. The interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed. Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfD_S or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval. The RfD is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan. For compounds for which there is sufficient evidence of carcinogenicity, q_1^*s have been computed, if appropriate, based on oral and inhalation data if available.

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PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with DDT. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the TOXLINE, CANCERLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to May, 1987. Secondary sources of information have also been relied upon in the preparation of this report and represent large-scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) sources have been extensively utilized:

U.S. EPA. 1980a. Ambient Water Quality Criteria for DDT. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Water Regulations and Standards, Washington, DC. EPA-440/5-80-038. NTIS PB81-117491.

U.S. EPA. 1986a. The Assessment of the Carcinogenicity of Dicofol (Kelthane), DDT, DDE, and DDD (TDE). Prepared by the Office of Health and Environmental Assessment, Carcinogen Assessment Group, Washington, DC for the Hazard Evaluation Division Office of Pesticide Programs. EPA 600/6-86/001. NTIS PB87-110904.

The intent in these assessments is to suggest acceptable exposure levels for noncarcinogens and risk cancer potency estimates for carcinogens whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data were limited in scope, which tended to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard or risk associated with exposure to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfD_S (formerly AIS) or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan). This type of exposure estimate has not been extensively used, or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is assumed. Animal data used for RFD_S estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure. These values are developed for both inhalation (RfD_{SI}) and oral (RfD_{SO}) exposures.

The RfD (formerly AIC) is similar in concept and addresses chronic exposure. It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980b) for a discussion of this concept]. The RfD is route-specific and estimates acceptable exposure for either oral (RfD_O) or inhalation (RfD_I) with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for identifying reportable quantities and the methodology for their development is explained in U.S. EPA (1984).

For compounds for which there is sufficient evidence of carcinogenicity RfD_S and RfD values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980b). Since cancer is a process that is not characterized by a threshold, <u>any</u> exposure contributes an increment of risk. For carcinogens, q_1^*s have been computed, if appropriate, based on oral and inhalation data if available.

ABSTRACT

In order to place the risk assessment evaluation in proper context, refer to the preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate interpretation of and use of the quantitative estimates presented.

U.S. EPA (1986a) estimated a human q_1^* of 0.34 $(mg/kg/day)^{-1}$ for orally administered DDT based on the geometric average of potencies from six separate studies.

Data are not available for the evaluation of the potential carcinogenicity of DDT following inhalation exposure.

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LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
BCF	Bioconcentration factor
bw	Body weight
CAS	Chemical Abstract Service
CS	Composite score
K_{oc}	Soil sorption coefficient
ppm	Parts per million
RfD	Reference dose
RfD_I	Inhalation reference dose
RfD_O	Oral reference dose
RfD_S	Subchronic reference dose
RfD_{SI}	Subchronic inhalation reference dose
RfD_{SO}	Subchronic oral reference dose
SER	Smooth endoplasmic reticulum
STEL	Short-term exposure limit
TLV	Threshold limit value
TWA	Time-weighted average

1. ENVIRONMENTAL CHEMISTRY AND FATE

The physical and chemical properties and environmental fate of DDT (CAS No. 50-29-3 for p,p'-DDT and 789-02-6 for o,p'-DDT) are as follows:

Chemical class:	pesticide
Molecular weight:	354.5
Vapor pressure:	1.9×10^{-7} mm Hg for p,p'-DDT at 20°C (IARC, 1974) 1.5×10^{-7} mm Hg for p,p'-DDT at 20°C 5.5×10^{-6} mm Hg for o,p'-DDT at 30°C (Callahan et al., 1979)
Solubility in Water (25°C):	<1.2-25 µg/ℓ for p,p'-DDT 26-85 µg/ℓ for o,p'-DDT (Callahan et al., 1979; IARC, 1974)
Solvents:	Very soluble in fats and most organic solvents (IARC, 1974)
Log octanol/water partition coefficient:	3.98-6.19 (Callahan et al., 1979)
BCF:	10^3 to 10^4 (Callahan et al., 1979)
K_{oc}:	2.4×10^5 (Sabljic, 1984)
Half-life in Water:	56 days for p,p'-DDT and 110 days for o,p'-DDT in lake water (Zoeteman et al., 1980)
Soil:	2->15 years (NLM, 1987)
Air:	6 days (Crosby and Mollanen, 1977)

DDT is the common name approved by the International Standards Organization for the technical product that contains ~65-80% of p,p'-DDT, ~15-21% o,p'-DDT and a small amount of several other compounds (IARC, 1974). The mobility of DDT in soils has been studied by various authors (U.S. EPA, 1980a) and has been reported to be extremely low. Therefore, the leaching of DDT from soil is expected to be very slow, particularly in soil

with high organic carbon content. Nevertheless, DDT has been detected in groundwater samples. In a study of groundwater in New Jersey, the detection frequency was 8% for p,p'-DDT and 11% for o,p'-DDT (Page, 1981). On soil surfaces, DDT will be subject to photooxidation and volatilization. Results of a field monitoring study in Kenya indicate that DDT has a volatilization half-life of 110 days (NLM, 1987).

DDT will adsorb very strongly to sediment and will bioconcentrate significantly in fish. DDT may evaporate or undergo photooxidation from water surfaces. Under anaerobic conditions DDT may be susceptible to biodegradation; DDD and DDE are primary degradation products (NLM, 1987). The half-life of DDT in lake water was estimated to be 56-110 days. In river water, the half-life is usually an order of magnitude faster than in lake water (Zoeteman et al., 1980). Evaporation from water surfaces can be relatively rapid (NLM, 1987).

The half-life of DDT in the atmosphere is uncertain. DDT is probably lost from the atmosphere by washout, fallout or photochemical degradation (Spencer, 1975). The photolytic half-life for the transformation of DDT to DDE and DDD in the atmosphere can be estimated to be 6 days (Crosby and Moilanen, 1977). The fact that DDT has been found to participate in long distance aerial transport (Callahan et al., 1979) indicates that it has a relatively long half-life in the atmosphere.

2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL ANIMALS

2.1. ORAL

DDT and metabolites ingested are contained primarily in fat-bearing foodstuffs, and absorption of dietary DDT is estimated to be 95% of the absorptive values for these dietary fats (Jensen et al., 1957). Over 65% of the labeled DDT and metabolites were recovered in the bile collected from rats for 9 days following DDT ingestion (Jensen et al., 1957). More DDT is absorbed in rats when it is dissolved in digestible vegetable oils than when it is suspended in water or dissolved in indigestible mineral oils (Keller and Yeary, 1980).

In humans, the absorption of DDT follows the same pattern as the absorption of dietary fat; that is, absorption is relatively slow. However, absorption appears to be complete after 24 hours (Morgan and Roan, 1977).

2.2. INHALATION

Pertinent data regarding the absorption of DDT by inhalation were not located in the available literature.

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

3.1. SUBCHRONIC

3.1.1. Oral. Subchronic oral studies in rats are summarized in Table 3-1. Laug et al. (1950) exposed rats to different levels of DDT (1-50 ppm) in the food and examined the histology of the liver 15-27 weeks after the start of treatment. No effects were reported at an exposure of 1 ppm; however, at all the higher exposure levels (5-50 ppm), hepatic cell hypertrophy appeared to be dose-related and minimal alterations in liver histology were reported at an exposure of 5 ppm (Laug et al., 1950). Cameron and Cheng (1951), however, observed no histopathologic alterations in the livers of rats fed diets containing DDT at 350 ppm for 33-60 weeks. Hart and Fouts (1965) reported increased liver microsomal enzyme activity in rats at 5 and 50 ppm. No increase in liver microsomal activity was observed in rats fed 0.2 ppm for 1-13 weeks (Kinoshita et al., 1966). Ortega et al. (1956a,b) reported ultrastructural changes at 5 and 15 ppm in livers of male rats, but liver function was not affected in rats fed 400 ppm or less.

3.1.2. Inhalation. Pertinent data regarding the subchronic inhalation of DDT could not be located in the available literature.

3.2. CHRONIC

3.2.1. Oral. Chronic oral studies with DDT are summarized in Table 3-2. Exposure of rats to 200 ppm DDT in the food for 2 years resulted in increased liver weight in the females (Fitzhugh and Nelson, 1947; Fitzhugh, 1948). At higher doses (400-800 ppm), the liver alterations became more severe and were present in both sexes. Mortality occurred at 800 ppm. Liver lesions were present at all dose levels tested, the lowest of which was 10 ppm (Fitzhugh and Nelson, 1947; Fitzhugh, 1948). In the study by Treon and Cleveland (1955), male rats exposed to 25 ppm DDT in the food for 2 years and 3 generations had increased liver weights. Durham et al. (1963)

TABLE 3-1

Subchronic Oral Toxicity of DDT in Rats*

Dose (ppm)	Duration of Exposure	Sex	Number Used	Effects	Reference
50 10 5 1	15-27 weeks	M/F	75/75	Hepatic cell hypertrophy was definitely present at dose levels of 50 and 10 ppm, and minimally present at 5 ppm. No effects were reported at 1 ppm.	Laug et al., 1950
350	33-60 weeks	NR	NR	No histopathologic alteration in the exposed as compared with the control group.	Cameron and Cheng, 1951
50 5	3 months	NR	NR	Liver microsomal enzyme activity was increased at both exposure levels.	Hart and Fouts, 1965
15 5	2-18 months	NR	NR	Males had ultrastructural alterations (proliferation of SER and concentric membrane arrays) in the liver at both exposure levels.	Ortega et al., 1956a,b
0.2	1-13 weeks	NR	NR	Liver microsomal enzyme activity was not increased.	Kinoshita et al., 1966

*DDT isomer not reported

NR = Not reported

TABLE 3-2

Chronic Oral Toxicity of DDT

Isomer*	Dose (ppm)	Duration of Exposure	Species	Sex	Number Used	Effects	Reference
Technical	800 600 400 200 100 50 10 0	2 years	rat/ Osborne- Mendel	M/F M/F M/F M/F M NR NR M/F	24/24 24/24 24/12 24/12 12 NR NR 24/12	At 800 ppm there were increased mortality and liver lesions. Increased liver weight occurred at 200 ppm for females and at higher doses for both males and females. No second generation offspring survived in animals exposed to 600 ppm. A reduction in survival of preweanling rats occurred at DDT levels of >50 ppm. Liver lesions were present at all dose levels, but no reproductive effects were reported at exposures of 10 ppm.	Fitzhugh and Nelson, 1947; Fitzhugh, 1948
NR	25 12.5 2.5 0	2 years/ 3 generations	rat	M/F M/F M/F M/F	40/40 40/40 40/40 40/40	Males had increased liver weights at an exposure level of 25 ppm. Although size of the litter and the number of pregnancies remained unaffected by DDT, the mortality of the offspring during the first 21 days of life was increased at all exposure levels.	Treon and Cleveland, 1955
Technical p,p'-DDT	200 200	3.5-7.5 years	monkey	NR	NR	No observed effects reported.	Durham et al., 1963
Technical	3200 2000 400 0	39-40 months	dog	M/F M/F M/F M/F	7/7 2/2 1/1 1/1	No effects were observed at 400 ppm, but liver damage occurred at 2000 ppm and was more severe at 3200 ppm.	Lehman, 1952, 1965
p,p'-DDT	1000 500 0	44/48 weeks	hamster	M/F M/F M/F	25-30/ 25-30 25-30/ 25-30 79	Increased mortality as well as nervousness and convulsions were observed in exposed animals.	Agthe et al., 1970
Technical	1000 500 250	18 months	hamster	M/F M/F M/F	30/30 30/30 30/30	Increased liver weight and enzyme (glucose-6-phosphate dehydrogenase) activity and decreased lifespan were reported.	Graillot et al., 1975
p,p'-DDT	500 250 100	lifespan	hamster	NR	NR	No observed effects on growth or survival rate.	Cabral and Shubik, 1977

*Technical DDT consists of ~77.1% p,p'-DDT, 14.9% o,p'-DDT, 0.3% p,p'-DDD, 0.1% o,p'-DDD, 4.0% p,p'-DDE, 0.1% o,p'-DDE and 3.5% unidentified compounds (U.S. EPA, 1980a).

NR = Not reported

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reported that no effects were observed in monkeys exposed to 200 ppm DDT in the food for 3.5-7.5 years. Lehman (1952, 1965) reported no effects in dogs fed a diet containing 400 ppm, but liver damage occurred at ≥2000 ppm and was severe at 3200 ppm. In a study by Agthe et al. (1970), hamsters were exposed to DDT at 500 or 1000 ppm in the diet and nervousness, convulsions and increased mortality were reported in exposed animals; Graillot et al. (1975) reported increased liver weights at exposure levels ≥250 ppm; Cabral and Shubik (1977) reported no effects on the growth or survival rate of hamsters exposed to 100, 250 and 500 ppm of DDT in the food.

3.2.2. Inhalation. Pertinent data regarding the chronic toxicity of inhaled DDT could not be located in the available literature.

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

3.3.1. Oral. When pregnant mice were exposed to 1 mg/kg bw on days 10, 12 and 17 of gestation, morphologic changes were seen in the gonads and the fertility of the offspring, especially females, was reduced (McLachlan and Dixon, 1972). Although no teratogenesis was observed, 2.5 mg/kg given daily to pregnant mice was significantly embryotoxic, as well as blastotoxic and fetotoxic (Schmidt, 1973). Similarly in rabbits, increased resorption, premature delivery and reduced fetal growth, but no teratogenicity, were caused by exposure to 50 mg/kg DDT on days 7, 8 and 9 of pregnancy (Hart et al., 1971).

Longer-term reproduction studies are summarized in Table 3-3. When rats were exposed to 7 ppm DDT in the diet for 60 days before mating and for the duration of pregnancy, fertility was decreased and the number of resorptions increased, but there was no evidence of teratogenicity (Green, 1969). Although there have been no reports of any teratogenic effects of DDT, with the possible exception of ringtail occurring in rats exposed to 200 ppm DDT in the diet (Ottoboni, 1969), DDT has consistently caused a decrease in

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TABLE 3-3

Reproductive Studies

Isomer*	Dose (ppm)	Duration of Exposure	Species	Sex	Number Used	Effects	Reference
Technical	7	120 days	mouse/ BALB/c and CFW	NR	NR	No effects on reproduction were reported.	Hare and Good, 1967
p,p'-DDT,	15	2 generations	rat	NR	NR	No effects on reproduction were reported.	Ruby et al., 1971
o,p'-DDT,	15			NR	NR		
or Technical	15						
	1	175 days		NR	NR		
p,p'-DDT	500	6 months	rat	NR	NR	No effects were seen at the 20 ppm dose level. Growth of offspring was severely depressed at the 200 ppm dose level, and all offspring died within 10 days of birth when the animals were exposed to 500 ppm p,p'-DDT.	Clement and Okey, 1974
	200			NR	NR		
	20			NR	NR		
	0			NR	NR		
o,p'-DDT	1000	6 months	rat	NR	NR	The only effects were decreased fertility and growth in exposed animals seen at the 1000 ppm dose level.	Clement and Okey, 1974
	200			NR	NR		
	20			NR	NR		
	0						
Technical	150	8-36 weeks	rat	F	NR	An exposure level of 150 ppm caused reproductive failure. At 75 ppm, the number of pups/litter was not changed, but there was a decreased number of pregnant females.	Jonsson et al., 1975
	75			F	NR		
NR	7	2 generations	rat/ Sprague-Dawley	F	131	None of the rats in the second generation were able to get pregnant. There was decreased fertility and increased mortality in the first generation. No effect on the incidence of abnormal embryos.	Green, 1969
	0			F	396		
Technical	200	2 generations	rat/ Sprague-Dawley	F	NR	No reproductive disturbance was seen in exposed animals.	Ottoboni, 1969
Recrystallized DDT	25	2 years/ 3 generations	rat/ Carworth Farms	M/F	40/40	Although the size of the litter and the number of pregnancies remained unaffected by DDT, the mortality of the offspring was increased at all exposure levels.	Treon and Cleveland, 1955
	12.5			M/F	40/40		
	2.5			M/F	40/40		
	0			M/F	40/40		
Technical	250	2 generations	mouse	NR	NR	At an exposure of 250 ppm, there was increased mortality in the neonates, and reduced lifespan. Tremors and convulsions occurred in some animals.	Tomatis et al., 1972
	50						
	10						

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TABLE 3-3 (cont.)

Isomer*	Dose (ppm)	Duration of Exposure	Species	Sex	Number Used	Effects	Reference
Technical	250	4 generations	mouse/ BALB/c	NR	NR	No effects on reproduction were reported.	Terracini et al., 1973a,b
	20	2 generations	mouse/ BALB/c	NR	NR		
NR	250	6 generations	mouse	NR	NR	No reproductive effects were seen at exposure levels of 25 ppm. At an exposure level of 100 ppm, lactation was reduced and mortality of the offspring increased. The severity of the effects produced at 100 ppm were greatly increased at 250 ppm.	Keplinger et al., 1968
	100			NR	NR		
	25			NR	NR		
p,p'-DDT	343	5 times/week, 14 months	dog/ beagle	M/F	4/3	Decreased male libido and delayed female estrus were reported, as well as infertility, reduced lactation and mammary gland development, and increased maternal and fetal mortality.	Deichmann et al., 1971; Deichmann and MacDonald, 1971
Technical	400	3 generations	dog/ beagle	NR	NR	Except that estrus occurred earlier in exposed dogs than in controls, there were no observed effects on reproduction. However, liver weights were consistently higher in pups born to DDT-treated dams.	Ottoboni et al., 1977
	200						
	40						

*Technical DDT consists of ~77.1% p,p'-DDT, 14.9% o,p'-DDT, 0.3% p,p'-DDD, 0.1% o,p'-DDD, 4.0% p,p'-DDE, 0.1% o,p'-DDE and 3.5% unidentified compounds (U.S. EPA, 1980a).

NR = Not reported

reproductive capacity in mice (Keplinger et al., 1968), rats (Fitzhugh and Nelson, 1947; Fitzhugh, 1948; Treon and Cleveland, 1955; Clement and Okey, 1974; Jonsson et al., 1975) and dogs (Deichmann et al., 1971; Deichmann and MacDonald, 1971). Some studies reported no observed effects on reproduction in mice (Ware and Good, 1967), rats (Duby et al., 1971) and dogs (Ottoboni et al., 1977).

3.3.2. Inhalation. Pertinent data regarding the teratogenicity of inhaled DDT were not located in the available literature.

3.4. TOXICANT INTERACTIONS

Although there is widespread concern about the synergistic interaction of DDT with other potentially hazardous chemicals, this interaction has been studied with only a few chemicals. Weisburger and Weisburger (1968) reported that 10 mg/day of DDT in rats, which caused no hepatoma by itself, significantly increased the incidence of hepatomas caused by the ingestion of 1 mg/day N-fluorenacetamide (2-AAF). DDT is known to be a strong inducer in the mixed function oxidase system and 2-AAF has been demonstrated to be metabolized by a mixed function oxidase system to the hydroxy intermediate, which is carcinogenic; therefore, it was postulated that DDT exerted its influence by stimulating the hepatic mixed function oxidase system (Weisburger and Weisburger, 1968). After evaluating the interaction of DDT (200 ppm), aramite (200 ppm), methoxychlor (1000 ppm), thiourea (50 ppm) and aldrin (5 ppm), however, Deichmann et al. (1967) concluded that the chemicals did not act in an additive manner and, in fact, may have interacted antagonistically. Co-administration of 100 ppm DDT and 5 ppm dieldrin in mice resulted in an increase in liver tumor in males. However, in both male and female mice the histological characteristics of the liver tumors were more malignant after simultaneous exposure to DDT and dieldrin (Walker et al., 1972).

4. CARCINOGENICITY

4.1. HUMAN DATA

4.1.1. Oral. A group of prison volunteers ingested daily doses of DDT (3.5 mg/man/day or 35 mg/man/day) for 21.5 months (Hayes et al., 1971). No ill effects ascribed to DDT ingestion were reported 4-5 years after the start of the experiment.

4.1.2. Inhalation. Human data regarding the carcinogenicity of DDT have been collected from occupational exposure, which occurs chiefly through inhalation. In occupational exposures where doses ranged from an estimated 14-42 mg/man/day for 17.5-8 years (Ortelee, 1958) and 17.5-18 mg/man/day for an average of 15 years (range, 11-19 years) (Laws et al., 1967), no increased incidence of cancer was reported.

4.2. BIOASSAYS

4.2.1. Oral. The U.S. EPA (1986a) recently estimated the carcinogenic potency of DDT to humans based on a number of oral studies on rats and mice. These studies, as well as others that were considered for quantitative risk assessment, are summarized briefly in Table 4-1. A fuller description of these studies is available in U.S. EPA (1986a). The carcinogenicity of DDT has been tested extensively in mice, rats and hamsters. An NCI study reported by Innes et al. (1969) found increased incidence of hepatomas in male and female mice exposed to DDT beginning at 7 days of age. At first the DDT was introduced by gavage; after weaning at 4 weeks, the DDT was incorporated in the diet. In addition to liver tumors, females had an increased incidence of lymphomas (Innes et al., 1969).

Tarjan and Kemeny (1969) studied five generations of BALB/c mice exposed to DDT at a level of 2.8-3.0 ppm in the diet. A variety of tumors accounted for the increased incidence of cancer in exposed (28.7%) as compared with

TABLE 4-1

Oral Carcinogenicity of DDT

Vehicle	Dose	Length of Treatment	Length of Experiment	Species	Sex	Number Tested	Effects	Reference
NR	0 ppm 3.0 ppm	lifespan	5 generations	mouse/BALB/c	M/F M/F	406 683	Combined tumor incidence across 5 generations: lung tumors (16.9% treated, 1.2% control), lymphomas (4.8% treated, 1.0% control) and leukemias (12.4% treated, 2.5% control) occurred in the mice exposed to DDT.	Tarjan and Kemeny, 1969
Gelatin/diet	control 46.4 mg/kg/day, days 7-28 then 140 ppm, 4-81 weeks	81 weeks	NR	mouse/I[a]	M/F M/F	79/87 18/18	About 30% of the females died during treatment. Hepatomas occurred in 11/18 male and 4/18 female mice exposed to DDT, whereas only 8/79 male and 0/87 female controls had hepatomas.	Innes et al., 1969
Gelatin/diet	control 46.4 mg/kg/day, days 7-28 then 140 ppm, 4-81 weeks	81 weeks	NR	mouse/Y[b]	M/F M/F	90/82 18/18	About 30% of the females died during treatment. Hepatomas occurred in 7/18 male and 1/18 female mice exposed to DDT, whereas only 5/90 male and 1/82 female controls had hepatomas.	Innes et al., 1969
NR	0 ppm 2 ppm 10 ppm 50 ppm 250 ppm	lifespan	2 generations	mouse/CF1	M/F M/F M/F M/F M/F	113/111 124/105 104/124 127/104 103/90	The incidence of hepatomas was significantly increased ($p<0.01$) in both males and females exposed to 250 ppm DDT. When the animals were aged past 60 weeks, the increased incidence of liver tumors was significant ($p<0.01$) at all dose levels in males, but not females.	Tomatis et al., 1972
NR	0 ppm 50 ppm 100 ppm	112 weeks	NR	mouse/CF1	M/F M/F M/F	47/47 32/30 32/32	Liver tumors in mice on diets containing DDT at a dose of 0, 50 or 100 ppm occurred in 13, 37 and 53% of the males, and 17, 50 and 76% of the females, respectively.	Walker et al., 1972
NR	0 ppm 100 ppm	110 weeks	NR	mouse/CF1	M/F M/F	45/44 30/30	Liver tumors in mice on diets containing 0 or 100 ppm DDT occurred in 24 and 80% of the males and 23 and 96% of the females, respectively. Malignant liver tumors occurred in 4.4 and 30% of the males and 0 and 40% of the females.	Thorpe and Walker, 1973
NR	0 ppm 2 ppm 10 ppm 50 ppm 250 ppm	lifetime	6 generations	mouse/CF1	M/F M/F M/F M/F M/F	328/340 354/339 362/355 383/328 350/293	Cumulative incidence of hepatomas, males: 29.5, 50.5, 50.0, 55.9, 86.0% for 0, 2, 10, 50 and 250 ppm, respectively. Cumulative hepatomas, females: 4.7, 3.5, 9.0, 13.1, 65.5% for 0, 2, 10, 50 and 250 ppm, respectively.	Turusov et al., 1973

TABLE 4-1 (cont.)

Vehicle	Dose	Length of Treatment	Length of Experiment	Species	Sex	Number Tested	Effects	Reference
NR	0 ppm 2 ppm 20 ppm 250 ppm	2 generations	lifespan	mouse/ CF1	M/F M/F M/F M/F	107/131 112/136 106/128 106/121	Only liver tumors occurred more frequently in treated as compared with control animals. Male mortality caused by DDT toxicity was increased only in the group receiving a dose of 250 ppm. In males, those on diets of 0, 2, 20 and 250 ppm of DDT had incidences of liver tumers combined across 2 generations of 2/107, 3/112, 1/106, 15/106. For females, the corresponding incidences were 0/131, 0/135, 1/128 and 71/121.	Terracini et al., 1973a,b
NR	0 ppm 250 ppm	15 and 30 weeks	65, 95 and 120 weeks	mouse/ CF1	M/F M/F	481 713	Incidence of hepatomas in males treated for 15 weeks or 30 weeks with DDT and killed 65, 95 and 120 weeks after the start of the experiment was 13/60, 25/60, 25/60 and 38/60, 41/60 and 37/60, respectively. Corresponding values for controls were 12/70, 24/83 and 33/98. When females were treated for 15 weeks or 30 weeks with DDT and killed at 65, 95 and 120 weeks after the start of the experiment, the incidence of hepatomas was 3/60, 11/60, 5/60 and 4/54, 11/65 and 11/54, respectively. Corresponding control values for females were 0/69, 0/72 and 1/90.	Tomatis et al., 1974; Tomatis and Turusov, 1975
NR	0 ppm 22 ppm 44 ppm 0 ppm 87 ppm 175 ppm	78 weeks	93 weeks	mouse/ B6C3F1	M M M F F F	20 ~50 ~50 20 ~50 ~50	Mortality was significantly increased in treated females and the increase appeared dose-related. No other toxic or carcinogenic effects were seen.	NCI, 1978
Oil	0 ppm 100 ppm 200 ppm 400 ppm 600 ppm 800 ppm	2 years	NR	rat/ Osborne-Mendel	M/F M M/F M/F M/F M/F	24/12 12 24/12 24/12 24/24 36/24	The authors concluded that there was an increased incidence of liver tumor formation, but did not relate the effect to dose levels or sex, and did not provide any statistical analysis. Treatment began at weaning.	Fitzhugh and Nelson, 1947
NR	0 ppm 80 ppm 200 ppm	2 years	NR	rat/ Osborne-Mendel	M/F M/F M/F	30/30 30/30 30/30	No difference in tumor incidence between treated and control groups, except for bronchogenic carcinomas which occurred in 2/60 controls, 8/60 rats fed DDT at 80 ppm and 0/60 rats fed 200 ppm.	Delchmann et al., 1967; Radomski et al., 1965
NR	0 ppm 500 ppm	lifetime	lifetime	rat/ Wistar	M/F M/F	35/32 45/45	Increased incidence of liver tumors were seen in males (13/38, 35%) and females (15/28, 56%). No liver tumors were seen in controls.	Rossi et al., 1977

TABLE 4-1 (cont.)

Vehicle	Dose	Length of Treatment	Length of Experiment	Species	Sex	Number Tested	Effects	Reference
NR	15 mg/rat, 5 days/week by gavage	1 year	18 months	rat/ Fischer	M/F	15/15	No liver tumors nor signs of hepatotoxicity were seen, and no data were provided on the occurrence of other tumors.	Weisburger and Weisburger, 1968
NR	0 ppm 321 ppm 642 ppm 0 ppm 210 ppm 420 ppm	78 weeks	111 weeks	rat/ Osborne-Mendel	M M M F F F	20 -50 -50 20 -50 -50	No increase in tumor incidence or signs of toxicity were noted for DDT.	NCI, 1978
NR	0 ppm 125 ppm 250 ppm 500 ppm	lifetime	lifetime	rat/MRC Portion (Wistar derived)	M/F M/F M/F M/F	38/38 30/30 30/30 38/38	The incidence of hepatomas in males was 1/38, 0/30, 1/30 and 2/30 for the 0, 125, 250 and 500 ppm groups, respectively. Corresponding incidences for females were 0/38, 2/30, 4/30 and 7/38.	Cabral et al., 1982a
NR	0 ppm 125 ppm 250 ppm 500 ppm	NR	NR	hamster	M/F M/F M/F M/F	40/39 30/28 31/28 39/40	No liver tumors were seen in hamsters at any feeding level. There was a significant trend in total number of tumor-bearing females: 7.5, 16.6, 25.8 and 28.2% for 0, 125, 250 and 500 ppm, respectively.	Cabral et al., 1982b
NR	0 ppm 1000 ppm	NR	NR	hamster	M/F M/F	31/42 35/36	No increased incidence of liver tumors was seen. Incidences of adrenal adenomas were significantly elevated in females, but not males. Incidence for males: 0 ppm, 8/31; 1000 ppm, 14/35 and for females: 0 ppm, 2/42; 1000 ppm, 10/36.	Rossi et al., 1983

[a]C57Bl/6 females mated with C3H/Anf males

[b]C57Bl/6 females mated with AKR males

NR = Not reported

(3.2%) groups. Lung carcinoma, which occurred in 116 of the 196 animals with tumors, was the predominant type. Leukemia was found in 23 females and 21 males of the 196 animals that developed tumors. Tumors were also observed in the liver, kidney, spleen, ovary and other organs. The authors emphasized that the transplacental and translactational exposure to DDT that occurred during the experiment may have had an important, but unquantified, effect upon the results.

Under the auspices of IARC, Tomatis et al. (1972), Terracini et al. (1973a,b), Turusov et al. (1973) and Shabad et al. (1973) investigated DDT carcinogenicity in mice. Several multigeneration studies were conducted in which mice were exposed continuously to DDT, including transplacentally and translactationally. Tomatis et al. (1972) found that mice of both sexes exposed to 250 ppm DDT had a significantly higher incidence of hepatomas. When the mice exposed to lower doses of DDT (2-50 ppm) were allowed to age past 60 weeks, the males, but not the females, had a significantly higher incidence of hepatomas. In another experiment, Tomatis et al. (1974) demonstrated that hepatoma formation was dose-dependent and that exposure to DDT early in life may result in tumor formation in the aging animal even after removal of the source of DDT. Terracini et al. (1973a) found that the incidence of hepatomas was increased in BALB/c mice exposed to DDT. In addition, the mice exposed transplacentally and translactationally had an even higher incidence of liver tumors than the mice exposed after weaning only.

Walker et al. (1972) and Thorpe and Walker (1973) reported an increased incidence of liver tumors in CF1 mice exposed to DDT in their food for 2 years. They divided the liver lesions into two histological types. Subsequent analysis by Reuber (1974, 1976) classified the lesions as hepatocellular carcinomas and preneoplastic lesions.

The NCI (1978) bioassay reported no carcinogenic effect from DDT exposure, although the mortality of the female mice was significantly increased in a dose-related manner. The dose levels, however, were low in comparison with other bioassays.

In rats exposed to 100-800 ppm DDT in the diet for 18 months, the dose-related changes in the liver included hypertrophy of centrolobular hepatic cells, hyalinization of the cytoplasm and focal necrosis (Fitzhugh and Nelson, 1947). More than half (111 of 192) of the rats died during the experiment. Of the 81 that remained alive at the end of the treatment period, 4 had liver carcinomas and 11 had preneoplastic hepatic lesions. No liver pathology was observed in the control animals (Fitzhugh and Nelson, 1947). Rossi et al. (1977) reported an increased incidence of liver tumors in rats exposed to 500 ppm DDT in their diets. Other studies on the carcinogenicity of DDT administered to rats in doses ranging from 210-642 ppm (NCI, 1978; Weisburger and Weisburger, 1968; Deichmann et al., 1967; Radomski et al., 1965) reported no increased incidence of liver tumors.

None of the bioassays in hamsters revealed an increased incidence of tumors in DDT exposed animals (Agthe et al., 1970; Cabral and Shubik, 1977; Graillot et al., 1975), and Graillot et al. (1975) reported a marked dose-related decrease in the incidence of lymphosarcoma in the DDT exposed hamsters as compared with controls.

4.2.2. Inhalation. Pertinent data regarding the carcinogenicity of inhaled DDT were not located in the available literature.

4.3. OTHER RELEVANT DATA

Additional qualitative evidence for the carcinogenicity of DDT in animals has been obtained from *in vivo* two-stage initiation/promotion studies and from genotoxicity studies. The weight-of-evidence from genotoxicity studies can be summarized as follows. No increase in the number of reverse mutants was

caused by DDT in Salmonella typhimurium (strains TA1535, TA1536, TA1537 and TA1538) or Escherichia coli (strains B/r try WP2, and WP2 try hcr), in the presence or absence of rat liver microsomes (Shirasu et al., 1976; Marshall et al., 1976). DDT caused no significant increase in recombination mutants in Bacillus subtilis (Shirasu et al., 1976), in recessive lethal mutants in Neurospora crassa (Clark, 1974; Luers, 1953) or in reverse mutation frequency in a host-mediated assay in Salmonella typhimurium in mice (Buselmaier et al., 1972). Chromosomal aberrations have been reported in cultivated rat-kangaroo cells (Palmer et al., 1972) and human lymphocytes (Lessa et al., 1976), but not in rat cells (Legator et al., 1973). An increase in dominant lethal mutations was caused by DDT in Drosophila melanogaster (Clark, 1974), the Swiss mouse (Clark, 1974) and the rat (Palmer et al., 1972), but not in the CF1 mouse (Wallace et al., 1976) or the ICR/Ha mouse (Epstein et al., 1972).

In the in vivo two-stage initiation/promotion studies, DDT exhibited tumor promotion activity in conjunction with a known number of initiators, including 2-acetylaminofluorene (2-AAF), 2-acetamitophenanthrene (AAP), and trans-4-acetylaminostilbene (trans-AAS). In all of the two-stage initiation/promotion studies, animals were treated with lifetime dietary exposure to DDT following an initial, brief exposure to a known tumor initiator. Liver tumor incidence was significantly increased in rats treated for 18 days with 0.02% 2-AAF then followed by 0.05% DDT, when compared with those of the sham-control rats and rats treated for 18 days with 0.02% 2-AAF (Peraino et al., 1975). In another study using rats, DDT caused the acceleration of 2-AAP-initiated mammary tumors and ear duct tumors in male but was negative for liver tumor promotion (Scribner and Mottet, 1981). Rats initiated with trans-AAS were found to have precancerous conditions in many tissues, including the liver, but only mammary tissue responded with tumors when promoted with exposures to DDT in the diet (Hilpert et al., 1983).

4.4. WEIGHT OF EVIDENCE

DDT has been associated with liver tumors in mice (Innes et al., 1969; Tomatis et al., 1972; Terracini et al., 1973a,b) and rats (Rossi et al., 1977), and lymphomas and pulmonary tumors (Tarj'an and Kem'eny, 1969) in mice. Based on inadequate evidence for carcinogenicity in humans and sufficient evidence of carcinogenicity in animals, DDT is most appropriately classified as a Group B2 - Probable Human Carcinogen following the scheme adopted by the Carcinogen Assessment Group (U.S. EPA, 1986b). This is consistent with the analysis by CAG (U.S. EPA, 1986a).

5. REGULATORY STANDARDS AND CRITERIA

The EPA banned all use of DDT, except for public health emergency, in 1972 (U.S. EPA, 1980a).

The WHO (1971) recommended a maximum interim ADI in food of 0.005 mg/kg/bw for DDT. The ACGIH (1986a) recommended a TLV-TWA of 1 mg/m³ based on analogy with lindane, which was judged to be twice as toxic as DDT (ACGIH, 1986b). A STEL was not recommended. OSHA (1985) recommended an occupational standard PEL of 1 mg/m³.

6. RISK ASSESSMENT

6.1. SUBCHRONIC REFERENCE DOSE (RfD_S)

DDT is known to be an animal carcinogen and data are sufficient for computing a q_1^*. Therefore, it is inappropriate to calculate an RfD_{SO} or RfD_{SI} for DDT.

6.2. REFERENCE DOSE (RfD)

DDT is known to be an animal carcinogen and data are sufficient for computing a q_1^*. Therefore, it is inappropriate to calculate an RfD_O or RfD_I for DDT.

6.3. CARCINOGENIC POTENCY (q_1^*)

6.3.1. Oral. The Carcinogen Assessment Group has developed a quantitative estimate of the carcinogenic potency of DDT (U.S. EPA, 1986a). The studies selected for quantitative evaluation were Tarjan and Kemeny (1969), Turusov et al. (1973), Terracini et al. (1973a), Thorpe and Walker (1973), Tomatis and Turusov (1975), Cabral et al. (1982a) and Rossi et al. (1977).

The data used for estimation of a q_1^* from the Tarjan and Kemeny (1969) study as shown in U.S. EPA (1986a) are presented in Table 6-1. Group sizes were considered inadequate for reliable evaluation in the F_1 and F_2 generations. A potency estimate of 7.27 $(mg/kg/day)^{-1}$ was calculated based on the geometric mean of the potencies for generations F_3-F_5 for lung cancers and leukemia.

The data used for estimation of a q_1^* from the Turusov et al. (1973) study as shown in U.S. EPA (1986a) are presented in Table 6-2. A geometric mean of the potencies across six generations for liver tumors of 0.80 $(mg/kg/day)^{-1}$ for males and 0.42 $(mg/kg/day)^{-1}$ for females was estimated.

TABLE 6-1

Incidence of the Most Commonly Occurring Malignant Tumors in Each of Five Generations of BALB/c Mice Fed DDT[a]

Site/Dose Group	Incidence by Generation[b] (combined male and female) (%)				
	F_1	F_2	F_3	F_4	F_5
Lung (carcinomas)					
Control	0/3 (00.0)	0/39 (00.0)	3/51 (5.9)	0/144 (00.0)	2/169 (1.2)
3 ppm DDT[c]	2/10 (20.0)	10/35 (28.5)	13/69 (18.8)	41/264 (15.5)	50/305 (16.4)
Significance[d]	ND	p=0.001	p=0.007	p<0.002	p<0.001
q_1^*[e]	ND	18.78	9.09	7.45	7.37
q_1^*[f]	ND	17.20	9.95	7.16	7.68

TABLE 6-1 (cont.)

Site/Dose Group	Incidence by Generation[b] (combined male and female) (%)				
	F_1	F_2	F_3	F_4	F_5
Leukemia					
Control	2/3 (66.6)	1/39 (2.6)	0/51 (00.0)	3/144 (2.1)	4/169 (2.4)
3 ppm DDT[c]	4/10 (40.0)	2/35 (5.7)	11/69 (15.9)	35/264 (13.2)	33/305 (10.8)
Significance[d]	ND	p=0.924	p=0.008	p<0.001	p=0.002
q_1*[e]	ND	4.67	9.48	5.79	4.50
q_1*[f]	ND	5.01	8.98	6.22	4.83

[a]Source: U.S. EPA, 1986a

[b]Number of animals with tumors/number of animals examined (percent). The F_1 generation contained too few effective animals for reliable statistical analysis.

[c]The human equivalent doses are calculated by multiplying the ppm values by 0.13 and then by the cube root of 0.030/70. 3 ppm DDT to BALB/c mice = 0.029 mg/kg bw/day for humans. The DDT was given to the mice for lifetime in the diet every day, so no time correction is necessary.

[d]Beneath each dose group incidence is the p value for the comparison of the dose group incidence with that of the control group. The F_1 generation was not analyzed.

[e]The q_1*s were calculated using the human equivalent dose. The index values assume that DDT contamination in the control diets was zero.

[f]The q_1* were calculated using a level of 0.20 ppm DDTr (combined DDT-related residues) in the control feed, as reported by the authors.

ND = Not determined

TABLE 6-2

Incidence of Benign Liver Tumors in Each of Six Generations of CF-1 Mice Fed DDT[a]

Sex/Dose Group	Benign Liver Tumor Incidence by Generation (%)[b]					
	Parental	F_1	F_2	F_3	F_4	F_5
Males						
Control	14/60 (24)	13/60 (21)	20/60 (34)	21/60 (35)	16/60 (26)	23/60 (39)
2 ppm[c]	26/60 (44)	29/60 (48)	38/60 (63)	30/60 (50)	34/60 (57)	25/60 (42)
10 ppm	32/60 (53)	28/60 (47)	33/60 (55)	36/60 (60)	24/60 (40)	26/60 (44)
50 ppm	27/60 (45)	35/60 (58)	41/60 (69)	36/60 (60)	32/60 (53)	28/60 (47)
250 ppm	46/60 (76)	51/60 (85)	53/60 (89)	53/60 (89)	57/60 (95)	48/60 (80)
q_1^{*}[d]	0.572	0.873	0.935	0.878	1.096	0.598

TABLE 6-2 (cont.)

Sex/Dose Group	Benign Liver Tumor Incidence by Generation (%)[b]					
	Parental	F_1	F_2	F_3	F_4	F_5
Females						
Control	3/60 (5)	2/60 (3)	1/60 (2)	2/60 (3)	4/60 (7)	5/60 (8)
2 ppm[c]	3/60 (5)	1/60 (2)	3/60 (5)	5/60 (9)	0/60 (0)	0/60 (0)
10 ppm	2/60 (3)	8/60 (13)	8/60 (13)	3/60 (5)	5/60 (8)	6/60 (10)
50 ppm	8/60 (13)	7/60 (12)	8/60 (13)	9/60 (15)	10/60 (16)	7/60 (11)
250 ppm	37/60 (61)	43/60 (71)	31/60 (52)	40/60 (67)	48/60 (80)	38/60 (64)
q_1^*[d]	0.372	0.471	0.369	0.434	0.526	0.370

[a]Source: U.S. EPA, 1986a

[b]Number of animals with tumors/number of animals examined (percent). The effective number of animals was given by Turusov et al. (1973) as 50-60; 60 has been used for every group because the exact number was not given.

[c]The human equivalent doses are calculated by multiplying the ppm values by 0.13 and then by the cube root of 0.030/70 (=0.0753949). No adjustment for time was made because these were lifetime tests and CF-1 mice were fed DDT continuously during that time. For example, human equivalent doses are as follows: 2 ppm = 0.0196, 10 ppm = 0.0980, 50 ppm = 0.4900 and 250 ppm = 2.45 mg/kg bw/day.

[d]The q_1^*s of the upper-bound limits in units of $(mg/kg\ bw/day\ of\ dietary\ exposure)^{-1}$ were calculated using the multistage model.

The data used for estimation of a q_1^* from the Terracini et al. (1973a) study as shown in U.S. EPA (1986a) are presented in Table 6-3. A geometric mean potency (q_1^*) of 0.082 $(mg/kg/day)^{-1}$ for liver tumors was calculated across sexes and two generations.

The data used for estimation of a q_1^* from the Thorpe and Walker (1973) study as presented in U.S. EPA (1986a) are shown in Table 6-4. The q_1^* values for the incidence of malignant liver tumors in males and females were calculated as 0.52 $(mg/kg/day)^{-1}$ and 0.81 $(mg/kg/day)^{-1}$, respectively.

The data used for estimation of a q_1^* from the Tomatis and Turusov (1975) study as presented in U.S. EPA (1986a) are shown in Table 6-5. The q_1^* values selected for benign liver tumors in males and females were 1.04 $(mg/kg/day)^{-1}$ and 0.49 $(mg/kg/day)^{-1}$, respectively, based on the 95-week sacrifice, because this duration most nearly approximates the expected lifetime of the mouse.

The data used for estimation of a q_1^* from the Cabral et al. (1982a) study are shown in Table 6-6. A q_1^* of 0.084 $(mg/kg/day)^{-1}$ was calculated for liver tumors in female rats. The data used for q_1^* estimation from Rossi et al. (1977) are also shown in Table 6-6. The q_1^* values for liver tumors in male and female rats of 0.16 and 0.27 $(mg/kg/day)^{-1}$, respectively, were calculated.

Table 6-7 presents a summary of the calculated potency estimates. Of these values, the q_1^* based on Tarj'an and Kem'eny (1969) was eliminated based on the Dixon statistical criterion for rejecting outliers (p=0.01) and the additional considerations that the study was from an unaudited laboratory and that the feed was contaminated with DDT. A geometric average of the values from the remaining six studies resulted in a final q_1^* estimate for DDT of 0.34 $(mg/kg/day)^{-1}$: $(0.80 \times 0.42 \times 0.082 \times 0.52 \times 0.81 \times 1.04 \times 0.49 \times 0.084 \times 0.16 \times 0.27)^{1/10} = 0.34$.

TABLE 6-3

Incidence of Benign Liver Tumors in BALB/c Mice Fed DDT During a 2-Generation Experiment[a,b]

Dose Group	Incidence of Benign Liver Tumors by Generation[c]		
	Males	Females	
	Parental + F_1	Parental	F_1
0 ppm	2/107 (1.9)	0/62 (0)	0/69 (0)
Trend[d]	p<0.001	p<0.001	p<0.001
2 ppm	3/112 (2.7)	0/63 (0)	0/73 (0)
20 ppm	1/106 (0.9)	1/61 (1.6)	0/67 (0)
250 ppm	15/106 (14.2)	28/63 (44.4)	43/58 (74.1)
q_1*[e]	0.074	0.080	0.094
High dose q_1*	0.086	0.324	0.718

[a]Source: U.S. EPA, 1986a

[b]Number of animals with tumors/number of animals examined (percent). Malignant tumors were not observed in liver.

[c]The numbers in the groups of males were reduced by fighting, so the 2 generations of males were pooled. Each high-dose group shown is statistically different from its control group (p<0.001). Other pairwise tests were not significant.

[d]Beneath the control incidence is the p value for positive trend in incidence over the dose levels.

[e]The q_1*s were calculated using the human equivalent dose. The "high dose q_1*" is the result of using only the controls and the high-dose groups in the calculations. The human equivalent doses are calculated by multiplying the ppm values by 0.13 and then by the cube root of 0.030/70 (=0.0753949). For example, 250 ppm = 2.45 mg/kg/day for humans.

TABLE 6-4

Incidence of Liver Tumors (Benign and Malignant) in CF-1 Mice Fed DDT for a Single Generation[a]

Dose Group	Incidence of Benign Liver Tumors[b]	Incidence of Malignant Liver Tumors[b]
Males		
Controls	11/45 (24%)	2/45 (4.4%)
100 ppm	23/30 (80%)	9/30 (30%)
q_1^*	ND	0.52
Females		
Controls	10/44 (23%)	0/44 (0%)
100 ppm	26/30 (87%)	12/30 (40%)
q_1^*	ND	0.81

[a]Source: U.S. EPA, 1986a

[b]Benign liver tumors in this study were referred to as "type a" and malignant liver tumors as "type b."

ND = Not determined

TABLE 6-5

Incidence of Benign Liver Tumors in CF-1 Mice Fed DDT for 15 or 30 Weeks and then Sacrificed at 65, 95 and 120 Weeks[a,b,c]

Dose Group	Males at Week			Females at Week		
	65	95	120	65	95	120
0 ppm[d]	12/70 (17)	24/83 (29)	33/98 (34)	0/69 (0)	0/72 (0)	1/90 (1)
250 ppm for 15 weeks[e]	13/60 (22) p=0.142	25/60 (42) p=0.040	25/60 (42) p=0.080	3/60 (5) p=0.097	11/60 (14) p<0.001	5/50 (10) p=0.034
250 ppm for 30 weeks[e]	38/60 (63) p<0.001	41/60 (68) p<0.001	37/60 (62) p<0.001	4/54 (7) p=0.034	11/55 (20) p<0.001	11/54 (20) p<0.001

TABLE 6-5 (cont.)

Dose Group	Males at Week			Females at Week		
	65	95	120	65	95	120
q_1^*[f] values						
all q_1^*	0.36	1.04	0.84	0.19	0.49	0.35
30 week	1.38	1.43	1.06	0.19	0.79	0.43

[a]Source: U.S. EPA, 1986a

[b]Number of animals with tumors/number of animals examined (percent).

[c]Some groups were exposed for 15 weeks; other groups were exposed for 30 weeks. All groups were sacrificed serially at 30, 65, 95 and 120 weeks.

[d]The human equivalent dose for 1 ppm for 15 weeks is 0.4084 mg/kg/day and for 30 weeks is 0.8168 mg/kg/day. The human equivalent doses are calculated by multiplying the ppm values by 0.13 and then by the cube root of 0.030/70 (=0.0753949). Adjustments for time consist of multiplying the 15-week dose by 15/90 and the 30-week exposure by 30/90.

[e]Beneath each dosed group incidence is the p value for comparison of the incidence in the dose group with that in the control group.

[f]The q_1^*s were calculated based on the human equivalent dose shown in footnote d. The term "all q_1^*" indicates that the dosed groups and the control group were used in the calculation. The "30 week" row contains the results of using only the 30-week exposure cancer data with the control cancer data.

TABLE 6-6

Incidence of Benign Liver Tumors in Rats Fed DDT[a,b]

Dose Group[e]	Cabral et al., 1982a[c]		Rossi et al., 1977[d]	
	Males	Females	Males	Females
0 ppm Trend[f]	1/38 (0) NS	0/38 (0) p=0.003	0/35 (0) NA	0/32 (0) NA
125 ppm	0.30 (0) NS	2/30 (6.7) NS	NA	NA
250 ppm	1/30 (3.3) NS	4/30 (13.3) p=0.033	NA	NA
500 ppm	2/38 (5.3) NS	7/38 (18.4) p=0.005	9/27 (33.3) p<0.001	15/28 (53.6) p<0.001
q_1*[g]	ND[h]	0.084	0.16	0.27

[a]Source: U.S. EPA, 1986a

[b]Number of animals with tumor/number of animals examined (percent).

[c]These were Portion (Wistar derived) rats.

[d]These were Wistar rats.

[e]The human equivalent doses are calculated by multiplying the ppm values by 0.0085499, which is 0.05 mg/kg/day (for rats) multiplied by the cube root of 0.350/70 (=0.0753949). No adjustment for time was made because rats were fed continuously for a lifetime.

[f]Beneath the control group incidence is the p value for a positive trend of incidences as the dose increases, when the p values is less than p=0.05, otherwise NS (not significant). Beneath each dosed group incidence is the p value for the comparison of the incidence in the dosed group with its control group when it is less than p=0.05, otherwise NS.

[g]The q_1*s were calculated using the human equivalent dose. For example, 500 ppm = 4.275 mg/kg/day for humans.

[h]Not calculated due to lack of statistical increase in hepatomas.

NS = Not significant; ND = not determined; NA = not applicable

TABLE 6-7

Summary of Quantitative Potency Estimates for DDT*

Species	Tumor Site	q_1^* (mg/kg/day)$^{-1}$		Reference
		Males	Females	
Mouse	lung/leukemia	7.27 (combined)		Tarjan and Kemeny, 1969
Mouse	liver	0.80	0.42	Turusov et al., 1973
Mouse	liver	0.082 (combined)		Terracini et al., 1973a
Mouse	liver	0.52	0.81	Thorpe and Walker, 1973
Mouse	liver	1.04	0.49	Tomatis and Turusov, 1975
Rat	liver		0.084	Cabral et al., 1982a
Rat	liver	0.16	0.27	Rossi et al., 1977

*Source: Adapted from U.S. EPA, 1986a

6.3.2. Inhalation. Pertinent data regarding the carcinogenicity of inhaled DDT could not be located in the available literature.

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APPENDIX

Summary Table for DDT

Carcinogenic Potency	Species	Experimental Dose/Exposure (mg/kg/day)	Effect	q_1^* $(mg/kg/day)^{-1}$	Reference
Inhalation	NA	NA	NA	ND	NA
RfD_{SI} (formerly AIS)					
RfD_I (formerly AIC)					
Oral	mice and rats	several dietary studies: 0.0196-2.45 mg/kg/day for mice and 1.06-4.27 mg/kg/day for rats	liver tumors	0.34	U.S. EPA, 1986a; Turusov et al., 1973; Terracini et al., 1973a; Thorpe and Walker, 1983; Tomatis and Turusov, 1975; Cabral et al., 1982a; Rossi et al., 1977
RfD_{SO}					
RfD_O					

NA = Not applicable; ND = not determined